OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-21-00762
Title: The “mitochondrial stress responses”: the “Dr. Jekyll and Mr. Hyde” of neuronal disorders
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COMMENTS TO AUTHORS

In this review summarizes the current knowledge of mitochondrial stress responses in neurological disorders. The review is in general very well written and the disposition is easy to follow as a reader. Unfortunately the authors multiple times not properly describe the original findings when referring to findings in experimental disease models vs human disease. The result of this is that ex vivo models and experimental models multiple times are referred to as human disease. Please correct this throughout.
I also find some overstatements and implications of original findings (often the authors own findings). This is more specified below and needs to be corrected throughout. I also lack some original findings which I have specified below.

Below I have specified my specific comments.

The manuscript provided lack numbering thus my page numbering starts on the page with the headline "introduction" = side 4

Page4Line7: Recently this was also reviewed by Pfanner et al 2019. (PMID: 30626975)
P4L56-61: please rephrase this sentence
P5L59: Here I miss citation of Li et al 2017 (PMID: 28934388)
P6L60: Here I miss description of findings by Sarzi et al 2012 (PMID: 23250881) and the introduction to a mouse model for human dominant optical atrophy via OPA1delTTAG.
P7L1-4 (whole paragraph): In addition to how mitofusion is connected to neurological disorders and apoptosis, I miss Ineichen et al 2020 (PMID: 23250881) describing how the interplay between neurons and myelin during homeostasis and demyelinating models.
P7L11: Remove "reactive oxygen species"
P7L36: Also via conjugation of GSH to toxic or reactive compounds eg 4-HNE. The protective effects against reactive aldehydes in neurons was originally shown by McCracken et al 2000 (PMID:11083227) and more recently by Carlstrom et al 2020 (PMID:32792491)
P10L53-55: For this paragraph i find it relevant that the authors specify in which cells the mitochondrial status was imbalanced. Above focus has been on neurons or other brain-resident cells. Here the authors cite studies conducted on mitochondrial status in peripheral cells. Better example of mitochondrial status imbalance in brain-resident cells is eg Qi et al 2006 (PMID: 16920708)
P10L58-60: This is a considerable overstatement. I would rephrase this. In a smaller MS cohort also markers of mitophagy have been detected. My main concern regarding this study is that I dont understand why mitophagy regulating peptides would end up in CSF/sera soley due to increased mitophagy. The reason why they are detected is due to cell death. This should be emphasized. However to state that itis directly involved in the MS pathology based on this study is an overstatement. Please rephrase.
P11L1-4: Same issue as above. Again this is a smaller cohort of patients and during active phases of MS disease it’s well known that multiple proteins and peptides are being elevated both in CSF ansd sera. The simplest explanation why many of these proteins/peptides are are being detected is solely due to cell death and not due to increased (in this case mitophagy). Again to me I can’t see by which

mechanism mitophagy markers are being increased in CSF/sera in the absence of cell death. Also here the authors provide no evidence that they not simply measuring cell death.

P11L12-15: Again I find it as an overstatement to say that this has been shown during MS progression. This article describes ex vivo models and in vivo demyelinating models which is not equal to MS. The data that is from MS is descriptive and cannot backup the current statement.

P11L23: "MS progression" - please clarify that the main findings described here comes from experimental models and not MS.

P15L25-33: Please rephrase this sentence, very long.

P15L51: please replace with "ALS"

P20L60: "MS-like disease" - To me it’s perfectly fine to use the term MS-like model instead of eae but my suggestion is to have a uniform vocabulary throughout this review describing when mention data from EAE/MS-like disease models or demyelinating in vivo models such as cup or LPC. I think it will improve the review and clarify to the reader. Especially the authors (as stated previously) need to be more careful when citing to experimental data and refer to it as human disease.